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DN

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/737, 457 03/12/97 CARDY

D 960670.0RI

EXAMINER

HM12/0413

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ART UNIT PAPER NUMBER

17

1644
DATE MAILED:

04/13/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/737,457	Applicant(s) Cardy et al.
	Examiner Lubet	Group Art Unit 1644

Responsive to communication(s) filed on Jan 11, 1999

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 1-3 and 5-24 is/are pending in the application.

Of the above, claim(s) 24 is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 1-3 and 5-23 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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1. This office action is in response to Paper 10 filed Jan. 11, 1999.
2. Examiner acknowledges the cancellation of claim 4 in the above mentioned paper 10. Claims 1-3, 5-23 and newly added claim 24 are under examination.
3. The text of those section of Title 35, U.S.C. not included in this action can be found in a prior office action.
4. Applicant has traversed the species requirement set forth in the previous office action arguing that the different chimaeric peptides claimed generically are sufficiently related that the claims should be examined as a unitary invention. This argument is not found to be persuasive for the reasons of record, and the election of species requirement is made final. Claims 1-3 and 5-23 are under examination as they read upon the elected species, a chimeric protein comprising anti-MHC-II binding portion, p53 effector portion and HIV tat translocation portion. Claim 24 is withdrawn from consideration as being drawn to the non-elected invention since the fusion protein claimed in claim 24 comprises pseudomonas exotoxin. Such a fusion protein is not the elected species of the invention.
5. Examiner acknowledges the filing a CRF and paper copy of CRF of sequence listing. The specification is objected to because specification does not disclose the SEQ ID NO: of the sequences disclosed on pages 10-11. Applicant is required to amend the specification to disclose such SEQ. ID. NO.'s.
6. Examiner acknowledges the amendment to the specification to disclose an abstract and to disclose "BRIEF DESCRIPTION OF THE FIGURES" heading on page 7 of the specification.
7. Examiner acknowledges amendment to the specification to refer to priority documents. Applicant should not refer to Great Britain priority documents and should amend the specification to delete reference to the Great Britain priority documents.

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8. (withdrawn) The rejection of claims 1-23 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.. Reasons are set forth below.

The rejection of claims 1 and 3 set forth in previous office action is withdrawn in view of the Applicant's persuasive response on page 7 of Paper 10.

The rejection of claim 6 set forth in previous office action is withdrawn in view of the Applicant's persuasive response on page 7 of Paper 10. It is noted that Applicant has indicated that the term "modulate" encompasses increasing and decreasing.

The rejection of claim 9 set forth in previous office action is withdrawn in view of the Applicant's persuasive response on pages 8-9 of Paper 10. It is noted that the term " capable of exerting an immunomodulatory" encompasses increases and decreases of the immune response.

The rejection of claim 1 set forth in previous office action is withdrawn in view of the Applicant's persuasive response on page 9 of Paper 10. It is noted that the peptide can be any length so long as it binds to the MHC binding groove.

9. (reiterated) A chimeric protein comprising anti-MHC II antibody-p53-HIV-TAT is not entitled to benefit of priority documents Great Britain 9409643.8 (filed 5/13/94) or Great Britain 94 17461.2 (filed Aug. 18, 1994) because there is no support for a such a chimeric protein in these priority documents. If Applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the specification.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

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11. (maintained) Claims 1-3 and 5-23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Donnelly *et al.* EP 0 532 090 A2 (issued Sept. 2, 1992), in view of Fawell *et al.* (PNAS 91: 1994), Murphy US 5,668,255 (issued Sep. 16, 1997, priority to Jun 27, 1991), Zimmerman *et al.* US 5,652,341 (issued Jul 29, 1997, priority to Dec. 4, 1992),, Lowenadler *et al.* (Mol. Immunology 29:1195, 1992), Noguchi *et al.* (PNAS 3171, April 1994) and Roemer *et al.* PNAS(90:9252, 1993).

EP 0532 090 A2 teaches chimeric peptides comprising a cellular recognition portion, *Pseudomonas* exotoxin translocating portion and an immunogenic peptide effector portion (see Claims 1-7 and abstract, in particular). EP 0532 090 A2 does not teach a chimeric protein in which the translocating domain is HIV TAT protein.

However, Fawell *et al.* teach that a chimeric protein comprising HIV TAT protein and β -galactosidase which can deliver heterologous macromolecules into cells such as endothelial cells, Kupffer cells or splenic macrophages (which are APC cells). Therefore it would have been *prima facie* obvious to one with skill in the art at the time of the invention to substitute the HIV TAT translocation domain for the *Pseudomonas* translocation domain of the chimeric protein taught by EP 0532 090 A2 with the expectation that such a molecule would deliver the immunogenic peptide to the target cell and that the molecule would be translocated into the cell. Thus these references in combination teach a chimeric protein comprising a cellular recognition domain--immunogenic peptide-- translocating domain in which the translocating domain is HIV TAT.

EP 0532 090 A2 does not teach that the cellular recognition domain of the chimeric protein is a anti-MHC II antibody or effective binding portion thereof. However, Murphy *et al.* teach a chimeric polypeptide comprising a translocation region and a cell binding region in which the binding region is an antigen binding portion of an immunoglobulin with specificity to an antigen expressed on a target cell (see abstract and column 3 line 14 through column 4, line 51, in particular). Zimmerman *et al.* teach a chimeric protein comprising a cellular binding portion and an antigen associated with a disease or an immunogenic epitope thereof, in which the cellular binding portion is specific for MHC Classes I and II such as beta 2-microglobulin or antibodies to cell surface proteins (see column 4, lines 46-55 , in particular). Therefore it would have obvious to one with skill in the art at the time of the invention to modify the chimeric protein taught by EP 0532 090 in view of Fawell *et al.* by substituting an anti-MHC II immunoglobulin for the cell binding portion taught by EP 0532 090 with the expectation that such a chimeric molecule would target MHC II bearing cells, including T cells and APC and that the polypeptide would be translocated into the cell.

Lowenadler *et al.* teach chimeric proteins comprising cellular binding portion (Ig-G binding component STaZZ), translocation portion (enterotoxin from *E. coli*) and immunogenic peptides which are repeats of an peptide comprising an immunodominant epitope of ovalbumin linked to an peptide derived from insulin like growth factor (see Figure 1 and abstract in particular).

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Lowenadler *et al.* teach that such a chimeric protein which elicits T and B cell responses to the immunogenic peptides (see abstract, Figures 2-3, and pages 1188-1189, in particular).

Therefore it would have been *prima facie* obvious to one with skill in the art at the time of the invention to modify the chimeric protein taught by the previously cited references to substitute repeats of the same peptide or a polypeptide effector portion comprising a plurality of different peptides for the immunogenic peptide effector portion of the chimeric protein taught by the prior art references with the expectation that such a polypeptide would induce immune responses to the immunogenic peptide effector portion of the chimeric protein.

Roemer *et al.* teach a chimeric protein in which comprises p53 effector portion and human estrogen receptor hormone binding portion. The human estrogen receptor hormone binding portion targets the chimeric protein to cells expressing estrogen receptors. Noguchi *et al.* teach that p53 is expressed on tumor cells and that CTL specific for p53 may be induced by immunizing with peptides derived from p53. Therefore it would have been *prima facie* obvious to one with skill in the art at the time of the invention to substitute p53 or fragments of p53 for the immunogenic peptide effector portion of the chimeric polypeptides taught by the prior art with the expectation that the polypeptide chimeric protein would be targeted to cells such as APC expressing MHC II and that an immune response, including CTL, to p53 would be elicited.

--Applicant's response on pages 10-14 of Paper 10 has been considered but is not persuasive.

Applicant's argument that EP 0532 090 does not teach the claimed invention because the cellular recognition portion and translocating portion are not from different portions is not persuasive because EP 0532 090 was used in combination with Fawell *et al.* to establish that the prior art teaches fusion protein comprising an immunogenic peptide and HIV TAT translocation.

The components of fusion protein taught by EP 0532 090 in view of Fawell *et al.* are derived from different sources.

Applicant's argument that there is no showing that the fusion protein taught by EP 0532 090 in view of Fawell *et al.* elicits an immune response is not persuasive. EP 0532 090 clearly teaches that use of peptide-translocation peptide fusion protein to elicit immune response (CTL) to the peptide component (see abstract and claims, in particular) and Fawell *et al.* teach HIV TAT-peptide fusion product may be used to stimulate class I major histocompatibility complex responses (see 668, in particular).

Applicant's argument that the HIV TAT- peptide fusion protein taught by EP0532 090 in view of Fawell does not target a particular cell type is acknowledged by the Examiner. The targeting component of the claimed fusion protein is taught by Murphy US 5,668,255 and Zimmerman *et al.* US 5,652,341. Applicant argues that the fusion proteins taught by Murphy or Zimmerman *et al.* are not internalized. However, Murphy and Zimmerman *et al.* were cited to teach the cell targeting component of the fusion protein, not the translocating portion.

Applicant's argument that the fusion protein (STaZZ-OVA-n-insulin like growth factor peptide) taught by Lowenadler *et al.* does not target a particular cell type because Sta epitopes do not target a particular cell type is not on target. The above reference has been revised to

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correct a typographical error (StaZZ is IgG binding domain) Lowenadler *et al.* was cited to teach that the prior art teaches fusion proteins to elicit immune responses to immunogenic peptide (ova) in which there are multiple copies of the immunogenic peptide component.

Applicant's argument that since a large number of references are cited, there is insufficient motivation to combine the references to obtain the claimed invention is not persuasive. The claimed fusion protein comprises three components (1) a immunogenic peptide (p53), (2) a translocation component(HIV Tat) and (3) cell targeting component (anti-MHC antibody component). The prior art clearly teaches fusion proteins comprising immunogenic peptide and translocating component. The prior art also clearly teaches a fusion protein comprising a immunogenic peptide and an anti-MHC cell targeting component. One with skill in the art would be motivated make a fusion component comprising the three component taught by the prior art with the expectation that the fusion protein comprising immunogenic peptide, translocating protein and cell targeting protein could be used to induce immune response to the immunogenic peptide.

The motivation to use p53 as the immunogenic peptide is also taught by the prior art since Noguchi *et al.* teaches the motivation to elicit an immune response (CTL) to p53 peptides.

Applicant's argument that proteins introduced externally to cells (APCs) are not efficiently taken up, processed and presented by MHC molecules is not supported by the instant specification. The specification on page 12 teaches that the claimed fusion protein (P53-HIV tat-anti-MHC) does not have an increased efficiency in elicitation of anti-p53 CTL since CTL response elicited by p53 alone is at least as potent as that elicited by the claimed invention.

12. Examiner believes that all pertinent arguments have been addressed.

13. **No claim is allowed.** Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Martha Lubet in Art Unit 1644 whose telephone number is (703) 305-7148. The examiner can normally be reached on Monday through Friday from 8:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973. The FAX number for this group is (703) 305-3014 or 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Martha T. Lubet

TC

THOMAS M. CUNNINGHAM
PRIMARY EXAMINER
GROUP 1800